REMARKS

The Office Action

Claims 1-20 are pending. Claim 14 stands rejected for indefiniteness. Claims 4-7, 16, and 18 stand rejected for obviousness over Greenwell (LE Magazine, May 2000). Claims 1-3, 12, and 17 stand rejected for obviousness over Yamamoto et al. (U.S. Patent No. 5,635,486; hereafter "Yamamoto"), Pischel et al. (U.S. Patent No. 6,503,951; hereafter "Pischel"), and Monti et al. (Pharmacology Biochemistry and Behavior 1995, 51:125; hereafter "Monti"). Claims 1-3, 8-15, 17, and 19-20 stand rejected for lack of enablement.

Support for the Amendments

Support for the compounds recited in claims 1, 12, 17, 22, and 27 is found, for example, on page 4, lines 20-26, page 5, lines 1-11, page 6, line 19, page 9, lines 12-17, and page 9, line 27 – page 10, lines 2. Support for the amendment to claim 1 is found, for example, on page 10, line 12. Support for the amendment to claim 12 is found, for example, on page 5, lines 24-25. Support for new claims 22-26 is found in claims 12-16. Support for new claim 27 is found in claim 8. Support for new claim 28 is found in claim 2, and support for new claim 29 is found in claim 5. Support for new claim 30 is found, for example, on page 12, lines 12-14. No new matter has been added.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 14 has been rejected as being indefinite based on it recitation of alcohol, caffeine, or cocaine "usage." This claim has been amended to delete "usage," and the rejection may be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 4-7, 16, and 18 stand rejected for obviousness over Greenwell, and claims 1-3, 12, and 17 stand rejected for obviousness over Yamamoto, Pischel, and Monti. Applicants traverse these rejections.

To support an obviousness rejection, the Office must put forth a *prima facie* case that meets the legal standard for obviousness found in M.P.E.P. § 2142. This section states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

In addition, the Office has the initial burden "to provide some suggestion of the desirability of doing what the inventor has done" (M.P.E.P. § 2142). This standard has not been met in the present case. The combined references fail to teach or suggest the invention, and there is no motivation to combine the cited references.

The Invention

Each of rejected independent claims 1, 12, and 17 requires the administration of one of the recited compounds to a mammal either to (1) normalize the mammal's sleep/wake cycle (claim 1), (2) treat the mammal's sleep disorder (claim 12), or (3) increase cognitive function in a sleep-deprived mammal (claim 17).

While each of these uses has a connection to lack of proper sleep, Applicants emphasize that, in order to support a *prima facie* case of obviousness, the prior art must teach or suggest the administration of one of the *recited compounds* for the *specific use* recited in the claims, rather than sleep in general. In the present case, the cited references do not meet this standard.

Greenwell

The Office has maintained the rejection of claims 4-7, 16, and 18 over Greenwell. In rejecting Applicant's arguments with respect to this reference, the Office has concluded, "the sleep normalizing effects are due to the choline component of the composition in the method claims." This however appears to be inadvertent overstatement of the reference's teachings. Greenwell, the only cited reference that recites CDP-choline, does not teach or suggest that choline is useful for normalizing the sleep/wake cycle. Indeed, Greenwell does not mention the sleep/wake cycle at all. Accordingly, a scientific basis to support the Office's statement is lacking. While

Applicant's agree that Greenwell discloses that "[o]ne of the lesser-known functions of acetylcholine is helping to maintain sleep," maintenance of sleep is not normalizing the sleep/wake cycle, as required by the claims and as discussed in Applicants' previous reply. In the present context, normalizing and maintaining are not synonymous. Normalizing the sleep/wake cycle means making the pattern of the periods when a mammal is awake and asleep conform to its norm or standard. In contrast, maintaining sleep means keeping a mammal asleep, and keeping a mammal asleep may, in fact, disrupt the sleep/wake cycle, as the mammal would remain asleep when it would normally be awake. In addition, claims 16 and 18 are directed to indications other than normalizing the sleep/wake cycle. Specifically, claim 16 is directed to the use of CDP-choline to treat a sleep disorder, and claim 18 is directed to the use of CDP-choline to increase cognitive function in a sleep-deprived mammal. Thus, any argument based on the sleep/wake cycle is inapplicable to these claims.

Moreover, the only motivation provided by the Office for arriving at Applicants' claimed invention is that "the effects of choline [have] been compared to CDP-choline to determine whether cognitive function has been increased. One skilled in the art would find this article suggestive of the fact that CDP-choline is effective for increasing cognitive function as well as the other functions discussed for choline alone that include inducing and maintaining sleep." Even accepting the Office's position arguendo, the proffered motivation is insufficient for claims 4-7 and 16. Instant claims 4-7 depend from claim 1, which is directed to a method of normalizing the sleep/wake cycle, and claim 16

depends from claim 12, which is directed to a method of treating a sleep disorder. Inducing and maintaining sleep differ significantly from normalizing the sleep/wake cycle or treating a sleep disorder, as instantly claimed. For example, some mammals suffering from sleep disorders, e.g., periodic limb movement, do not need assistance in falling or remaining asleep. Furthermore, as mentioned above, maintenance of sleep may disrupt the normal sleep/wake cycle of the mammal. Consistent with these differences, there is no evidence of record that connects maintaining or inducing sleep with normalizing a sleep/wake cycle or treating a sleep disorder, and the Office's reliance on Greenwell is therefore misplaced. As Greenwell does not disclose or provide any connection to the indications to which claims 4-7 and 16 are directed, it cannot teach or suggest the limitations of these claims, or motivate one skilled in the art to make the claimed invention.

In addition, Greenwell does not state that CDP-choline is effective for any indication, in contrast to the Office's assertion. Greenwell merely states that glyceryl-phosphorylcholine produces superior results to CDP-choline in patients with vascular dementia. Greenwell further states that glyceryl-phosphorylcholine "appears to be the best choline donor in the brain." Based on these statements, one skilled in the art would not find Greenwell suggestive of any use of CDP-choline, much less those instantly claimed.

Claim 18 is directed to a method of increasing cognitive function in a sleep-deprived mammal. Applicants emphasize that this claimed indication is distinct from

increasing cognitive function in general or in subjects with dementia. Thus, the Office must provide motivation to produce Applicants' claimed method of increasing cognitive function in the specified population rather than to produce any such increase. In addition, according to the Office, Greenwell teaches that choline maintains and induces sleep. Based on this reasoning, one skilled in the art would expect that administering choline to a sleep-deprived mammal would result in that mammal falling asleep, an outcome that is exactly opposite to an increase in cognitive function. Indeed, since falling asleep would decrease the mammal's cognitive function, Greenwell teaches away from Applicants' claimed method and cannot therefore provide any teaching, suggestion, or motivation with respect to the limitations of claim 18. Thus, based on the Office's reasoning, one skilled in the art would look for compounds other than choline to increase cognitive function in sleep-deprived mammals.

In sum, Greenwell does not teach or suggest the limitations of any of the rejected claims, and the Office has not provided any motivation from the prior art to produce the claimed invention. This basis for the rejection should be withdrawn.

Yamamoto, Pischel, and Monti

In a separate rejection, the Office has also relied on Yamamoto to supply teachings that "uridine and cytidine induce sleep"; on Pischel to supply teachings on creatine that are not disclosed in Yamamoto; and on Monti to teach "that Adenosine modulates sleep in Rats as an animal model for humans." As an initial matter, Applicants note that

Yamamoto actually teaches that cytidine *inhibits* sleep (col. 2, ll. 46-50). Also, Monti discloses that the two compounds studied therein modulate sleep *apnea* and decrease sleep efficiency (abstract). With respect to the relevance of the teachings of Pischel and Monti to claims 1 and 12, these claims have been amended to delete "creatine-containing compound," "adenosine-containing compound," and "an adenosine-elevating compound," and any teachings of these references are now moot with respect to those claims.

Claims 1 and 12

Amended claim 1 is directed to a method of normalizing the sleep/wake cycle of a mammal by oral administration of particular compounds. In contrast to amended claim 1, which is directed to *oral* administration, Yamamoto is directed to *ophthalmic* administration (see Abstract and specification generally). Yamamoto does not recommend oral administration and in fact states, "there is no report, except [with respect to melatonin and tryptophan], that the oral administration of the above described sleep adjusting substances derived from an organism is effective. This is because these substances have a disadvantage that they are easily metabolized in an organism and scarcely reach the region for adjusting the biological rhythm in the brain since they are derived from an organism. Therefore, it has been impossible to put these substances to practical use." (col. 2, ll. 23-31) Yamamoto thus fails to teach or suggest oral administration as instantly claimed. Moreover, Yamamoto clearly teaches away

from oral administration by stating that effective oral administration of these compounds is "impossible" (M.P.E.P. § 2145.05(III)). As neither Pischel nor Monti teaches oral administration of the claimed compounds, they cannot remedy the deficiencies of Yamamoto. The rejection of claim 1 for obviousness over the combination of Yamamoto, Pischel, and Monti may be withdrawn.

Amended claim 12 is directed to a method of treating a *sleep disorder*. With respect to this claim, the Office has not alleged that Yamamoto teaches or suggests the treatment of a *sleep disorder* by any means. Furthermore, neither Pischel nor Monti teach or suggest the use of the instantly claimed compounds for any indication, much less that claimed. Thus, the references when combined do not teach or suggest the limitations of claim 12 and cannot be used as the basis for a *prima facie* case of obviousness for this claim. The rejection may be withdrawn.

Claim 17

Amended claim 17 is directed to a method of *increasing cognitive function in a sleep-deprived mammal*. In order to render the invention of claim 17 obvious, the prior art must teach or suggest a method of increasing cognitive function in such a sleep-deprived mammal. The Office has not provided any support for a rejection of claim 17 based on Yamamoto, Pischel, or Monti. The Office has not alleged that Yamamoto, Pischel, or Monti, alone or in any combination, provide any teachings or suggestions relevant to the increase of cognitive function in a sleep-deprived mammal. Claim 17 is

not directed to the modulation of sleep or the induction of sleep. Thus, any motivation provided by the cited references with respect to these sleep issues are irrelevant to the patentability of claim 17. Again, the references fail to establish a *prima facie* case of obviousness, and the rejection should be withdrawn.

No Motivation Exists for Arriving at Applicants' Invention

In addition to the above deficiencies in the cited art, Applicants further point out that the stated motivation provided by the Office with respect to Yamamoto, Pischel, and Monti is insufficient to support the present obviousness rejection of claims 1-3, 12, and 17. In providing this purported motivation, the Office states, "all of the compounds, which are substituted in the instant application, are taught in the art, and the compounds are known to have sleep inducing properties." As discussed above, this statement is factually incorrect as the prior art teaches that cytidine inhibits sleep and certain adenosine analogs decrease sleep efficiency. The Office further relies on the statement that "one of ordinary skill in the art would be motivated to claim the methods as the applicant has in searching for new mean[s] to apply [the recited] compounds." This reasoning relies on Applicants' disclosure of the ability of the recited compounds to be useful for the claimed methods. Such reasoning is the result of impermissible hindsight analysis, as it finds no basis in the prior art but is instead entirely reliant on Applicants' discoveries and disclosure (M.P.E.P. § 2142). Furthermore, the standard for a *prima facie* case of obviousness is not that one skilled in the art would be motivated to search for

additional uses of known compounds, but that the prior art would motivate one skilled in the art to arrive specifically at the claimed method. In the present case, the prior art provides no motivation to combine the cited references to produce the instantly claimed methods, and, for this reason as well, the rejection should be withdrawn.

New Claims

New claims 21-30 have been added. Independent claim 22 is equivalent to original claim 12 with the exclusion of insomnia and sleep apnea. As none of the cited references discloses a sleep disorder covered by claim 22, the claim is allowable over the cited art. Independent claim 27 is equivalent to claim 8 rewritten in independent form. As claim 8 was not rejected over the art of record, claim 27 is allowable over the art.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-3, 8-15, 17, and 19-20 stand further rejected for lack of enablement. The independent claims have now been amended to recite compounds that include the specific cytidine, cytosine, uridine, creatine, and adenosine containing compounds referred to by the Office. Applicants traverse the rejection as applied to the amended claims.

M.P.E.P. § 2164.01(c) states: "If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph." Applicants have met this standard.

For each claimed indication, Applicants have provided exemplary compounds, such as cytidine, CMP, CDP, CTP, dCMP, dCDP, dCTP, CDP-choline, cytosine, uridine, UMP, UDP, UTP, triacetyl uridine, creatine, adenosine, AMP, ADP, ATP, S-adenosylmethionine, dipyridamole, propentofylline, and EHNA. Applicants have provided exemplary doses, formulations, and routes of administration of these compounds (pages 10-11). Furthermore, Applicants have provided scientific reasoning to support the effectiveness of the claimed compounds (page 6, line 25 – page 10, line 8). Methods are also known in the art to assess and, if necessary, alter bioavailability of these compounds (see, e.g., *Remington The Science and Practice of Pharmacy*, 20th ed., Chapter 53 and EP 0188647). Applicants have also provided adequate disclosure on how to assess therapeutic efficacy (Figures 1 and 2 and page 7, line 9 – page 8, line 2). Based on the totality of this information, one skilled in the art would be readily able to practice the claimed methods by administration of the compounds specified in Applicants' claims. This rejection should be withdrawn.

Information Disclosure Statements

Applicants note that the Forms PTO 1449 that were submitted with Information Disclosure Statements filed on December 2, 2004, February 10, 2005, June 16, 2005, and June 22, 2005 have not been initialed and returned, and hereby request that they be initialed and returned with the next Office action.

CONCLUSION

Applicants submit that claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying for three months, to and including March 12, 2006, and a check in payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 10 March 2006

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